8-2008

Impact of Universal Infant Immunization with Pneumococcal (Streptococcus pneumonia) Conjugate Vaccines in Alaska

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Methods: The medical literature concerning the epidemiology of invasive pneumococcal disease (IPD) and the effects of pneumococcal conjugate vaccine on the incidence, nasopharyngeal carriage, and antibiotic resistance of S pneumoniae was reviewed with special emphasis on the effects in the Alaska Native population.

Results: Alaska Native children experienced the highest incidence of IPD in the United States. The greatest difference in IPD was among children younger than 2 years for whom the annualized rate in Alaskan Native children (450/100,000 per year) was 3 times higher than for non-Native Alaskan children younger than 2 years who had rates similar to the overall US population.

In the first 3 years after beginning routine vaccination with PCV7 (2001-2003), overall IPD decreased 67 percent in Alaska Native children younger than 2 years (from 403.2 per 100,000 in 1995-2000 to 134.3 per 100,000 per year in 2001-2003, P <.001). However, between 2001-2003 and 2004-2006, there was an 82 percent increase in invasive disease in Alaska Native children younger than 2 years to 244.6/100 000 (P = .02). Since 2004, the IPD rate caused by nonvaccine serotypes has increased 140 percent compared with the prevaccine period (from 95.1 per 100,000 in 1995-2000 to 228.6 in 2004-2006, P = .001). During the same period, there was a 96 percent decrease in heptavalent vaccine serotype disease in Alaskan Native children. Serotype 19A accounted for 28.3 percent of invasive pneumococcal disease among Alaska children younger than 2 years during 2004-2006. There was no significant increase in nonvaccine disease in non–Native Alaska children younger than 2 years between 2001-2003 and 2004-2006.

During 1998–2004, the overall proportion of Alaska Native children <5 years of age colonized with S. pneumoniae remained stable>(59 percent at baseline and 61 percent in 2004), but there was an upward trend among adults >18 years of age (13 percent at baseline and 26 percent in 2004). This trend of increased nasopharyngeal carriage of S. pneumoniae in adults was observed among adults in all age classes. Among children <5 years of age who were colonized with S.>pneumoniae, the proportion with PCV7-type pneumococcal carriage decreased from 55 percent at baseline to 5 percent in 2004. Among adults colonized with S. pneumoniae, carriage of PCV7-type pneumococci decreased from 28 percent to 5 percent over this same period. Accordingly, because PCV7-type colonization decreased but overall colonization did not, there has been a marked increase in the proportion of adults with colonization due to non–PCV7-type pneumococci.

After beginning routine vaccination with PCV7, disease caused by penicillin-nonsusceptible strains among rural Alaska Natives decreased 81 percent (95% CI, 80-82%) among children under two years of age, and 49 percent among persons 65 years of age or older. Rates of resistant disease caused by vaccine serotypes fell 87 percent. Introduction of PCV7 into the routine infant immunization schedule in a community with a high prevalence of antimicrobial-resistant pneumococci (Anchorage, Alaska) appears to reduce transmission of PCV7 vaccine serotypes and cotrimoxazole nonsusceptible pneumococci but has no impact on overall carriage of pneumococci or carriage of penicillin nonsusceptible pneumococci.

In 2000, 93.7 percent of Alaskan homes had complete sanitation services (potable drinking water and safe wastewater disposal), which ranked Alaska last among US states. The percentage of homes with in-home water service in many parts of rural Alaska is significantly lower. Higher respiratory and skin infection rates were associated with a lack of in-home water service. Regions with a lower proportion of home water services had significantly higher hospitalization rates for pneumonia and influenza (RR = 2.5), skin or soft tissue infection (RR = 1.9), and respiratory syncytial virus (RR = 3.4 among those younger than 5 years) than did higher-service regions.

Conclusion: The PCV7 vaccine has nearly eliminated IPD caused by vaccine serotypes in Alaskan children younger than 5 years. However, this success has been diminished by a significant increase in non-PCV7 serotype IPD in Alaska Native children. Vaccination does not change the overall risk of pneumococcal carriage. However, it does reduce the acquisition of vaccine serotypes and increases the acquisition of nonvaccine serotypes. Although there has been an overall decline in the proportion of invasive isolates nonsusceptible to penicillin, increases in the rates of penicillin-nonsusceptible IPD caused by nonvaccine serotypes and by vaccine-related strains of S. pneumoniae (particularly 19A) have been noted.

The increase in replacement IPD also highlights the need for continued surveillance and other epidemiological investigations to monitor the effects of pneumococcal vaccines. Under antibody selective pressure, pneumococci can be expected to quickly evolve to circumvent vaccines that contain a limited number of serotypes. The only long-term solution to the problem is the development of a vaccine containing one or several protective protein antigens from pneumococcus.

In rural Alaska, basic improvements in housing, access to treated running water, instillation of sewage disposal and treatment facilities and improved economic opportunity would have far-reaching beneficial health effects. Although PCV7 has eliminated the disparity in vaccine-type IPD, health disparities among Alaska Natives are likely to continue until those disparities in living conditions are also eliminated.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

Subject Categories
Medicine and Health Sciences

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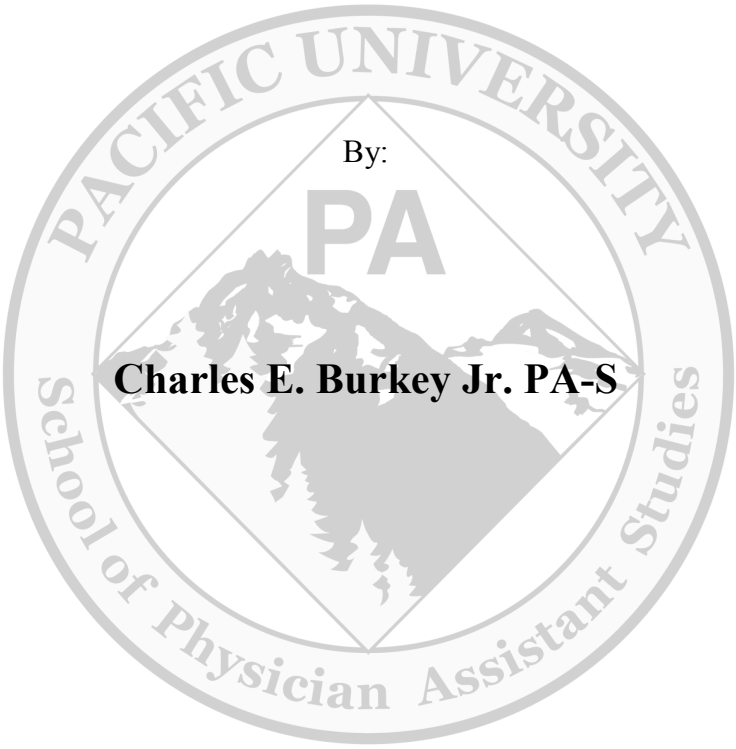

By:

Charles E. Burkey Jr. PA-S

A Clinical Research Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree August, 2008

Faculty Advisor**:** Latha Reddy MS, PA-C
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Biography

Charles Burkey Jr. is a resident of Kodiak, Alaska. He is a retired Fisheries Biologist from the Alaska Department of Fish and Game and pleased to be the senior member of the Class of 2008. He has been a volunteer EMT responding to some of the most remote places and in some of the most inclement weather in Alaska since 1990.

Abstract

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During 1998–2004, the overall proportion of Alaska Native children <5 years of age colonized with *S. pneumoniae* remained stable (59 percent at baseline and 61 percent in 2004), but there was an upward trend among adults >18 years of age (13 percent at baseline and 26 percent in 2004). This trend of increased nasopharyngeal carriage of *S. pneumoniae* in adults was observed among adults in all age classes. Among children <5 years of age who were colonized with *S. pneumoniae,* the proportion with PCV7-type pneumococcal carriage decreased from 55 percent at baseline to 5 percent in 2004. Among adults colonized with *S. pneumoniae,* carriage of PCV7-type pneumococci decreased from 28 percent to 5 percent over this same period. Accordingly, because PCV7-type colonization decreased but overall colonization did not, there has been a marked increase in the proportion of adults with colonization due to non–PCV7-type pneumococci.

After beginning routine vaccination with PCV7, disease caused by penicillin-nonsusceptible strains among rural Alaska Natives decreased 81 percent (95% CI, 80-82%) among children under two years of age, and 49 percent among persons 65 years of age or older. Rates of resistant disease caused by vaccine serotypes fell 87 percent. Introduction of PCV7 into the routine infant immunization schedule in a community with a high prevalence of antimicrobial-resistant pneumococci (Anchorage, Alaska) appears to reduce transmission of PCV7 vaccine serotypes and cotrimoxazole nonsusceptible pneumococci but has no impact on overall carriage of pneumococci or carriage of penicillin nonsusceptible pneumococci.

In 2000, 93.7 percent of Alaskan homes had complete sanitation services (potable drinking water and safe wastewater disposal), which ranked Alaska last among US states. The percentage of homes with in-home water service in many parts of rural Alaska is significantly lower. Higher respiratory and skin infection rates were associated with a lack of in-home water service. Regions with a lower proportion of home water services had significantly higher hospitalization rates for pneumonia and influenza (RR = 2.5), skin or soft tissue infection (RR = 1.9), and respiratory syncytial virus (RR = 3.4 among those younger than 5 years) than did higher-service regions.

Conclusion: The PCV7 vaccine has nearly eliminated IPD caused by vaccine serotypes in Alaskan children younger than 5 years. However, this success has been diminished by a significant increase in non-PCV7 serotype IPD in Alaska Native children. Vaccination does not change the overall risk of pneumococcal carriage. However, it does reduce the acquisition of vaccine serotypes and increases the acquisition of nonvaccine serotypes. Although there has been an overall decline in the proportion of invasive isolates nonsusceptible to penicillin, increases in the rates of penicillin-nonsusceptible IPD caused by nonvaccine serotypes and by vaccine-related strains of *S. pneumoniae* (particularly 19A) have been noted.

The increase in replacement IPD also highlights the need for continued surveillance and other epidemiological investigations to monitor the effects of pneumococcal vaccines. Under antibody selective pressure, pneumococci can be expected to quickly evolve to circumvent vaccines that contain a limited number of serotypes. The only long-term solution to the problem is the development of a vaccine containing one or several protective protein antigens from pneumococcus.

In rural Alaska, basic improvements in housing, access to treated running water, instillation of sewage disposal and treatment facilities and improved economic opportunity would have far-reaching beneficial health effects. Although PCV7 has eliminated the disparity in vaccine-type IPD, health disparities among Alaska Natives are likely to continue until those disparities in living conditions are also eliminated.

Keywords: invasive pneumococcal disease, *Streptococcus pneumoniae,* heptavalent pneumococcal conjugate vaccine, Alaska Natives.

Acknowledgements

To *Patricia*: Thank you for so bravely enduring the ‘widowhood’ of a Physician Assistant student’s wife. I am more than grateful for your encouragement, support and love. Your hard work keeping our home in order, allowing me to concentrate on the challenges of a strenuous academic program, is much appreciated.

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List of Abbreviations

13vP ..... 13-valent Pneumonococcal Conjugate Vaccine

ACIP ..... Advisory Committee on Immunization Practices

CDC ..... Centers for Disease Control and Prevention

COPD ..... Chronic Obstructive Pulmonary Disease

Hib ..... *Haemophilus influenzae* type b

IPD ..... Invasive Pneumococcal Disease

MnCC ..... Meningococcal Type C Conjugate Vaccine

NP ..... Nasopharyngeal

PCV7 ..... Heptavalent Pneumonococcal Conjugate Vaccine

PPV23 ..... 23-valent Polysaccharide Pneumococcal Vaccine

RSV ..... Respiratory Syncytial Virus

List of Appendices

Impact of Universal Infant Immunization with Pneumococcal (*Streptococcus pneumonia)* Conjugate Vaccines in Alaska

INTRODUCTION

Prior to 2000, *Streptococcus pneumoniae* (pneumococcus) was the most frequent cause of bacteremia, bacterial pneumonia, bacterial meningitis, sinusitis, and acute otitis media. There are an estimated 1.9 million deaths worldwide from acute respiratory illness in children younger than 5 years each year, many of these deaths are caused by *S pneumoniae*.[1] The highest rates of invasive pneumococcal disease (e.g. bacteremia, meningitis, or other infection of a normally sterile site) occur among young children, especially those aged <2 years. In 1988, the estimated incidence in the United States of invasive pneumococcal infections among children aged <12 months and 12-23 months were 165 and 203 cases/100,000 population, respectively, with peak incidence occurring among children aged 6-11 months (235/100,000). In contrast, incidence among persons of all ages and among persons aged ≥65 years were 24 and 61/100,000, respectively (Figure 1).[2]

In the United States, *S. pneumoniae* caused about 17,000 cases of invasive pneumococcal (IPD) disease annually in children younger than 5 years old, including 700 cases of meningitis and 200 deaths. Alaska Native children experienced the highest incidence of IPD in the United States. During the years 2004-2006, 57 percent of Alaska children younger than 5 years old presented with pneumonia. The greatest difference in IPD was among children younger than 2 years for whom the annualized rate in Alaskan Native children (450/100,000 per year) was 3 times higher than for non-Native Alaskan children younger than 2 years who had rates similar to the overall US population.[3, 4]

The objectives of this paper are to describe and compare the impact of universal infant immunization with 7-valent pneumococcal conjugate vaccine (PCV7) on invasive *S. pneumoniae* infections,

nasopharyngeal carriage, and antibiotic resistance in Alaskan Native and non-Native children and adults.

Introduction of the PCV7 into the routine childhood vaccination schedule in the United States in 2000 resulted in decreases in vaccine-type IPD and consequent decreases in all IPD among US children.[5] In the first three years after introduction (2001-2003), vaccine-type IPD rates decreased by 91 percent and the total IPD rates decreased by 65 percent among Alaskan Native children younger than 2 years old.[6] During the same periods, PCV7-type invasive disease in adults > 18 years of age decreased by 40 percent in Alaska (P<.001; CDC, unpublished data). Nasopharyngeal (NP) colonization of PCV7-type *S. pneumoniae* also declined in rural Alaska Native children and adults, however, the overall rate of NP colonization by *S. pneumoniae* remained unchanged.[6, 7]

The US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommends that the PCV7 vaccine be used for all children aged 2-23 months and for children aged 24-59 months who are at increased risk for pneumococcal disease (e.g., children with sickle cell disease, human immunodeficiency virus infection, and other immunocompromising or chronic medical conditions).[8] ACIP also recommends that the vaccine be considered for all other children aged 24-59 months, with priority given to a) children aged 24-35 months, b) children who are of Alaskan Native, American Indian, and African-American descent, and c) children who attend group day care centers. The ACIP's recommended vaccination schedule is to administer a total of 4 doses, one each at 2, 4, 6, and 12-15 months of age. Among children ages 24-59 months for whom 23-valent pneumococcal polysaccharide vaccine is already recommended, ACIP recommends vaccination with the new conjugate vaccine followed ≥2 months later, by 23-valent polysaccharide pneumococcal vaccine (PPV23).

The surface capsular polysaccharide of *S. pneumoniae* provokes a type-specific protective immune response and serves as the basis for serotyping of these organisms.[9] Ninety different pneumococcal serotypes have been identified. Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F are the most prevalent in children, accounting for between 60 and 80 percent of infections depending upon the area of the world. PCV7 (Prevnar®) contains 2 mcg of each saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F, and 4 mcg of serotype 6B per 0.5 mL conjugated to ~20 mcg/0.5 mL of diphtheria CRM197 carrier protein.

Although the previously licensed 23-valent pneumococcal polysaccharide vaccines (PNU-IMUNE® 23 marketed by Wyeth-Ayerst Laboratories and Pneumovax® 23 by Merck and Company) are effective in preventing invasive pneumococcal disease among older children and adults, these vaccines do not protect children aged <2 years, the age group with the highest rate of disease.[10] Furthermore, PPV23 does not decrease nasopharyngeal carriage, a substantial source of transmission of pneumococci.[2]

Prelicensure controlled clinical trials demonstrated that PCV7 is 94 percent efficacious against PCV7-type IDP.[11] A case of IPD is defined as isolation of pneumococcus from a normally sterile body site (e.g., blood or cerebrospinal fluid). A study conducted by Miernyk,[12] et al. indicated that PCV7 immunogenicity among Alaska Natives and American Indians was similar to immune system response among non-Alaska Natives/non-American Indians. In 2003, it was estimated that 29,599 cases of vaccine serotype IPD were prevented through routine immunization. Approximately two-thirds of these cases were prevented through herd immunity.[13]

Incidence of IPD caused by pneumococcal serotypes not included in PCV7 increased among children aged <5 years and adults aged >40 years, with a total of 4,721 projected additional cases of nonvaccine-type IPD in 2003. Net prevented cases were evenly distributed between the age group targeted for vaccination with PCV7 (12,786 prevented cases [51%]) and older children and adults

outside the target population (12,092 prevented cases [49%]). However, there are increasing data to suggest that universal immunization with PCV7 is changing the serotype patterns of IPD, NP colonization, and antibiotic resistance patterns.

Invasive Pneumococcal Disease in Alaska

Alaska's population of 626,932 (2000 US Census) includes 119,499 (19%) Alaska Native and American Indians, 5,304 of whom are younger than 2 years. Between 2003, and 2006, the proportion of 19- through 35-month-old Alaska Native children documented in electronic health records as having received at least 3 PCV7 doses increased from 88 percent to 96 percent.[14] Data tables from the National Immunization Survey for 2003 through 2004 for children aged 19 through 35 months estimated that 92.6 percent (95% confidence interval [CI], 84.7%-100%) of Alaskan Native children had received at least 3 doses of PCV7 compared with 64.6 percent (95% CI, 55.7%-73.5%) for non-Native Alaskans and 70.5 percent (95% CI, 69.5%- 71.5%) for the overall US population in this age group.[15]

In the first 3 years after beginning routine vaccination with PCV7 (2001-2003), overall IPD decreased 67 percent in Alaska Native children younger than 2 years (from 403.2 per 100,000 in 1995-2000 to 134.3 per 100,000 per year in 2001-2003, $P < .001$). This decline is similar to that reported elsewhere in the United States (69%).[6] However, between 2001-2003 and 2004-2006, there was an 82 percent increase in invasive disease in Alaska Native children younger than 2 years to 244.6/100 000 ($P = .02$). Since 2004, the IPD rate caused by nonvaccine serotypes has increased 140 percent compared with the prevaccine period (from 95.1 per 100,000 in 1995-2000 to 228.6 in 2004-2006, $P = .001$). During the same period, there was a 96 percent decrease in heptavalent vaccine serotype disease in Alaskan

Native children (Figure 2). Serotype 19A accounted for 28.3 percent of invasive pneumococcal disease among Alaska children younger than 2 years during 2004-2006 (Figure 3). There was no significant increase in nonvaccine disease in non–Native Alaska children younger than 2 years between 2001-2003 and 2004-2006.[14]

Compared with non–Native Alaska children, the RR of PCV7-type IPD for Alaska Native children younger than 5 years decreased from 2.84 (95% CI, 2.15-3.77) in the prevaccine period to 1.08 (95% CI, 0.34-2.94) in 2001-2006. In contrast, the RR for non-PCV7 type IPD in Alaska Native vs non–Native Alaska children younger than 5 years did not change: 3.91 (95% CI, 2.27-6.81) to 4.31 (95% CI, 2.93-6.41). Likewise, there was no change in the RR of all IPD for Alaska Native vs non–Native Alaska children from the prevaccine period (RR, 3.13; 95% CI, 2.47-3.96) to 2001-2006 (RR, 3.13; 95% CI, 2.46-4.87).[14]

In a group-randomized study,[16] PCV7 was given to 8,292 children younger than 2 years from the Navajo and White Mountain Apache Indian reservations; meningococcal type C conjugate vaccine (MnCC) served as the control vaccine. Vaccine schedules were determined by age at enrollment. They recorded episodes of invasive pneumococcal disease and serotyped isolates. Analyses were by intention to treat and per protocol. In the per protocol analysis of the primary efficacy group (children enrolled by 7 months of age) there were eight cases of vaccine serotype disease in the controls and two in the PCV7 group; in the intention-to-treat analysis there were 11 cases of vaccine serotype disease in the MnCC control group and two in the PCV7 group. After group randomization had been controlled for, the per protocol primary efficacy of PCV7 was 76·8 percent (95% CI –9·4% to 95·1%) and the intention-to-treat total primary efficacy was 82·6 percent (21·4% to 96·1%).

Alaska Native adults have age-adjusted invasive pneumococcal disease rates two- to three-fold greater than non-Native Alaskans.[4] The infection rate of IPD in Alaskan Native adults averaged 44.5 cases per 100,000 for the years 1986-2000. There was a total of 394 cases of which 69 (17%) were fatal. The majority of these infections occurred in persons with underlying conditions and behaviors associated with increased risk of IPD. Underlying conditions included heavy alcohol use (66%), smoking (61%) and COPD (25%).

The age-specific rate among urban Alaska Native adults 50–64 years (122.6/100,000/year) was five-fold higher than the rate in similarly aged US adults.[17] The higher rate of disease among urban compared with rural Alaska Native adults contrasts sharply with the rate for children. Annual IPD rates among Alaska Native children aged <2 years during 1991–1997, prior to availability of conjugate vaccine, were twice as high in rural areas (659/100,000) compared with urban areas (325/100,000).[18]

The overall effectiveness of PPV23 for prevention of IPD among Alaska Native adults in one study was 75 percent (95% CI: 27, 91%).[17] Recommendations for PPV-23 use in Alaska are expanded from national recommendations of the ACIP in that the age of universal immunization is 55 years and revaccination is recommended every 6 years.

Nasopharyngeal Carriage

S. pneumoniae is frequently present in the nasopharyngeal (NP) flora of healthy persons. Virtually all children are colonized with *S. pneumoniae* sometime during the first 2 years of life.[19] Since the addition of a heptavalent protein-polysaccharide conjugate vaccine to the routine childhood vaccination schedule in 2000, numerous studies have documented declining rates of colonization with

PCV7 serotypes and a lower incidence of PCV7-type invasive pneumococcal disease among young children.[14, 20 , 21]

Children are more commonly colonized with *S. pneumoniae* than are adults, and the highest rates of carriage are among preschool-aged children.[22] Adults living with preschool-aged children are more likely to be colonized than are adults who do not live with children[23] and adults who are in close contact with young children may be at greater risk for invasive disease than are adults who do not have contact with children.[24] PCV7 is currently not recommended for adults, but its widespread use in children could indirectly affect the rate of invasive disease in adults by reducing PCV7-type colonization through decreasing the transmission of PCV-type pneumococci from children. The decrease in rates of PCV7-type invasive disease among vaccinated children has been accompanied by a decrease in the rates of PCV7-type invasive disease among adults.[25]

Surveys of NP carriage were conducted in 8 villages in Alaska in 1998–2004.[25] Village populations ranged from 200 to 800 persons (total 3,868) of which over 95 percent were Alaskan Natives. *Streptococcus pneumoniae* isolates were characterized by serotype and antimicrobial susceptibility. Investigators analyzed trends in serotype distribution, antibiotic resistance, and factors associated with adult carriage of PCV7-serotype pneumococci before and after the introduction of PCV7 in 2001.

A total of 15,598 NP swabs were collected (mean 2,228 participants/year); annually, an average of 65 percent of children <5 years of age and 52 percent of adults >18 years of age living in the villages surveyed participated in the colonization study. Of the study participants, 309 (99%) of 311 children <5 years of age had received at least 1 dose of PCV7, and, as of 2004, 246 (79%) of these 311 children had been age-appropriately vaccinated.

During 1998–2004, the proportion of study participants colonized with *S. pneumoniae* remained stable among children <5 years of age (59 percent at baseline and 61 percent in 2004; *P*>.91 for trend; median percentage, 59 percent; range, 51%–61%), but there was an upward trend among adults >18 years of age (13 percent at baseline and 26 percent in 2004; *P* <.0001 for trend; median percentage, 18 percent; range, 13%–27%). This trend of increased carriage of *S. pneumoniae* in adults was observed among adults in all age classes.

Among children <5 years of age who were colonized with *S. pneumoniae,* the proportion with PCV7-type pneumococcal carriage decreased from 55 percent at baseline to 5 percent in 2004 (*P*<.0001 for trend; median percentage, 18 percent; range, 5%–55%). Among adults colonized with *S. pneumoniae,* carriage of PCV7-type pneumococci decreased from 28 percent to 5 percent over this same period (*P* value for trend, <.0001). This trend of decreased carriage of PCV7-type pneumococci among adults was observed for adults in all age classes. Accordingly, because PCV7-type colonization decreased but overall colonization did not, there has been a marked increase in the proportion of adults with colonization due to non–PCV7-type pneumococci.

This analysis of pneumococcal colonization among adults and children during the 3 years before and the 4 years after the introduction of pediatric PCV7 documents a significant, consistent decrease in PCV7-type pneumococcal colonization and a concomitant increase in non–PCV7-type pneumococcal colonization in both vaccinated children and unvaccinated adults. Colonization with serotype 19A increased in all age groups from less than 0.5 percent of colonized persons in 1998-2000 to 3 percent in 2003 and 15 percent in 2004 (*P*<.001 for trend).

A similar study was conducted on children presenting to 3 clinics in Anchorage, Alaska (a private clinic, a community clinic, and a clinic serving primarily children of Alaska Native descent) during the

winters of 2000, 2001, and 2003, as PCV7 was being introduced into the routine immunization schedule.[7] They obtained 1,350 nasopharyngeal swabs for culture from 1,275 children aged 3-59 months. The proportion of children who were up-to-date for age, with respect to PCV7 vaccination, increased from 0 percent in 2000 to 55 percent in 2002. Overall carriage of *S. pneumoniae* was stable over time (38% in 2000, 44% in 2001, 35% in 2003, [P = .41]). In 2000, 36 percent, 41 percent, and 37 percent of children at the community clinic, the private clinic, and the Alaska Native clinic, respectively, carried pneumococci ($P = .58$). Carriage of PCV7-type pneumococci decreased by 43 percent ($P<.0001$). Risk of carriage of PCV7-type pneumococci was lower in 2002 than in 2000, independent of vaccination status, suggesting an indirect effect of vaccination.

Replacement of PCV7 serotypes by nonvaccine serotypes in the nasopharynx and middle ear fluid has been reported in other populations.[26, 27, 28, 29] In Gambia, carriage of nonvaccine serotypes was found in 79 percent of children receiving 3 doses of a pneumococcal conjugate vaccine compared with 42.5 percent of control children.[27] In a pneumococcal conjugate vaccine trial in Finland, serotype replacement following vaccination resulted in an increase in acute otitis media caused by nonvaccine serotypes.[30] In 2004, Ghaffar et al.[31] hypothesized that the reduction of PCV7 type colonization and replacement by non- PCV7 colonization after a booster dose of vaccine suggested the possibility that widespread vaccination would result in replacement of pneumococci mainly by non-PCV7 serotypes.

Replacement IPD has not been demonstrated among Navajo children[32] or Australian aboriginal children.[33] These populations have similar characteristics of IPD and colonization. A major difference is that introduction of PCV7 occurred at a slower rate among Navajo children than among Alaska Native children (because of a vaccine trial)[16] and PCV7 was introduced later with a different schedule (3 primary doses with a booster of 23-valent pneumococcal polysaccharide vaccine at 18 months) in aboriginal children.[33]

Nasal carriage of *Staphylococcus aureus* in children appears to be inversely related to NP carriage of pneumococcal vaccine serotypes.[34] A potential concern with *S. aureus* carriage is the increasing frequency of community-associated methicillin-resistant *S. aureus* infections.

Antibiotic Resistance

The resistance of pneumococci to a variety of antimicrobial agents has become a worldwide health problem. Most surveillance data demonstrate a decline in the proportion of IPD cases nonsusceptible to penicillin and other antibiotics after PCV7 was added to the routine childhood immunization schedule.[14]

Worldwide, most antibiotic-resistant infections are caused by five of the seven serotypes in the 7-valent pneumococcal conjugate vaccine (6B, 9V, 14, 19F, and 23F).[35] In 1984, 24 percent of IPD isolates in the US were nonsusceptible to penicillin and five serotypes in PCV7 comprised 78 percent of such strains.[36] Rates of IDP caused by penicillin-nonsusceptible strains and strains not susceptible to multiple antibiotics peaked in 1999 and decreased by 2004, from 6.3 to 2.7 cases per 100,000 and from 4.1 to 1.7 cases per 100,000, respectively. Disease caused by penicillin-nonsusceptible strains decreased 81 percent (95% CI, 80-82%) among children under two years of age, and 49 percent among persons 65 years of age or older. Rates of resistant disease caused by vaccine serotypes fell 87 percent. Most resistant infections from serotypes not in the vaccine were caused by serotypes 6A and 19A. The increase seen in disease caused by serotype 19A was from 2.0 to 8.3 cases per 100,000 among children under two years of age. A concurrent drop in the rate of disease caused by serotype 6A suggests that the 6B vaccine component provides cross-protection against serotype 6A disease but that the 19F

component does not protect against 19A disease. Serotype 19A is included in a 13-valent pneumococcal conjugate vaccine that is in phase 3 clinical trials.

As part of the survey of NP carriage conducted in 8 villages in Alaska in 1998–2004, change in the antibiotic resistance of the *S. pneumoniae* isolates was also studied.[25] Among adults, the proportion of colonizing isolates that were resistant to penicillin decreased from 13 percent in 1998–2000 to 6 percent in 2004 ($P<.05$), whereas the percentage of isolates with intermediate susceptibility to penicillin increased from 12 percent in 1998–2000 to 19 percent in 2004 ($P<.01$). Adults were more likely to carry PCV7-type pneumococci if they lived with a child <5 years old or if they lived with a child who had not been age-appropriately vaccinated with PCV7.

In the NP carriage study of children aged 3-59 months in 3 Anchorage, Alaska clinics from 2000-2002, the carriage of cotrimoxazole nonsusceptible pneumococci decreased 38 percent (P=.02), not only among vaccinated children but also among unvaccinated children without recent use of antibiotics.[7] The NP carriage of penicillin nonsusceptible pneumococci remained stable over the course of 3 years (36% in 2000, 37% in 2001, 32% in 2002, [P = .48]). However, substantial clinic-to-clinic variation occurred; the prevalence of nonsusceptibility to penicillin among all carriers at the Alaska Native and community clinics decreased from 41 percent (45/109) in 2000 to 26 percent (29/110) in 2002 (relative decrease, 36%; $P = .06$). At the private clinic, nonsusceptibility to penicillin increased from 26 percent (16/62) in 2000 to 43 percent (21/49) in 2002, although this change was not statistically significant ($P=.15$). The proportion of penicillin-susceptible PCV7-type pneumococci decreased by 54 percent (P<.0003), whereas the proportion of PCN-NS PCV7-type pneumococci remained stable ($P=.38$).

Introduction of PCV7 into the routine infant immunization schedule in a community with a high prevalence of antimicrobial-resistant pneumococci (Anchorage, Alaska) appears to reduce transmission

of PCV7 vaccine serotypes and cotrimoxazole nonsusceptible pneumococci but has no impact on overall carriage of pneumococci or carriage of penicillin nonsusceptible pneumococci.

Although there has been an overall decline in the proportion of invasive isolates nonsusceptible to penicillin, increases in the rates of penicillin-nonsusceptible IPD caused by nonvaccine serotypes and by vaccine-related strains of *S. pneumoniae* (particularly 19A) have been noted.[37]

Discussion

The PCV7 vaccine has nearly eliminated IPD caused by vaccine serotypes in Alaskan children younger than 5 years. However, this success has been diminished by a significant increase in non-PCV7 serotype IPD in Alaska Native children. This phenomenon of replacement disease by non-PCV7 serotypes has not occurred to such a large extent in non-Native Alaskan children and children in the United States outside of Alaska. The initial decline in IPD in Alaska Native children <2 years old of 67 percent was similar to that seen elsewhere in the United States (69%). However, among Alaska Native children, a more than doubling of non-PCV7 serotype disease since 2003 reduced the overall decline to 41 percent.

Immunization against a pathogen has both a direct effect – protecting those successfully immunized from carriage of disease and an indirect effect (herd immunity) – providing protection against carriage or disease among unimmunized individuals by reducing transmission of the organism within the community. The direct effect of immunization is measured by controlled, randomized, clinical trials of vaccine efficacy, while the total effect of immunization (direct effect plus indirect effect on a

population) is usually estimated by observational and epidemiologic studies or community-randomized efficacy studies.[38]

Indirect benefits of PCV7 (i.e., cases prevented in unvaccinated persons) exceeded direct protective benefits among immunized children, with more than twice as many cases of VT IPD prevented indirectly as directly. The indirect effects of PCV7 are believed to be caused by decreased nasopharyngeal carriage of VT strains among immunized children, which results in decreased transmission to nonimmunized children and adults (i.e., herd immunity).[38, 39] The calculations of direct and indirect effects of the conjugate vaccine were based on data estimates from several sources, each with an associated margin of error; the calculations provide only crude estimates of the relative magnitudes of direct and indirect vaccine effects.

It cannot be determined to what extent the observed changes in disease rates and serotype distribution are due to the introduction of PCV7 or to other factors. The dramatic decrease in PCV7 type IPD accompanied by an increase in nonvaccine serotype disease suggests that these are vaccine effects. The relatively small population size in Alaska results in some of the subgroup comparisons being based on small numbers of cases and therefore having limited power to detect differences. These small sample sizes lead to higher between sample variability because a small number of IPD cases can have a significant impact on disease rates.

Another limitation in these Alaskan studies is that they likely underestimate IPD rates due to incomplete case ascertainment. Interest in pneumococcal disease could have improved IPD reporting for children since PCV7 introduction, and this could have created bias towards underestimating the vaccine effect. Also, colonization data (from convenience samples in 8 rural villages and 3 urban

clinics) may not be generalizable to all Alaskans. The small population studied limits the ability to detect trends in uncommon events.

Vaccination does not change the overall risk of pneumococcal carriage. However, it does reduce the acquisition of vaccine serotypes and increases the acquisition of nonvaccine serotypes. Pediatric vaccination with PCV7 has resulted in decreased PCV7-type pneumococcal carriage among adults and helps to explain recent decreases in the rate of PCV7-type IPD among adults. Although the nasal carriage of *Staphylococcus aureus* in children appears to be inversely related to NP carriage of pneumococcal vaccine serotypes, the fact that PCV7 vaccination does not change the overall rate of pneumococcal carriage may prevent significant increases in *S aureus* carriage.

The incidence of penicillin-resistant IDP has decreased markedly since the introduction of PCV7 into the routine infant immunization schedule. Five of the seven serotypes in PCV7 account for most of the antibiotic-resistant IPD infections.[36] Most resistant infections from serotypes not in the vaccine were caused by serotypes 6A and 19A. The incidence of serotype 19A-caused IPD has more than doubled in Alaska Native children <2 years of age since introduction of the PCV7 vaccine. One factor that may help diminish the future prevalence of antibiotic-resistant IPD infections is that the overall lower rates of IPD infections experienced since introduction of the PCV7 vaccine has lead to reduced use of antibiotics in younger children.

Two factors are thought to be responsible for the reduction in antibiotic-resistant strains following vaccination:[40] 1) immunization with PCV7 decreases acquisition of vaccine serotypes that are antibiotic-resistant, and 2) recipients of PCV7 receive less antibiotic therapy than nonvaccinated children, further reducing the selective pressure to acquire resistant strains.

The history of invasive *Haemophilus influenzae* type b (Hib) disease in Alaska is similar to that of IPD with the exception that significant replacement disease (non-*H influenza* type b serotypes) has not occurred.[41] Before infant vaccination starting in 1991, Alaska Native children experienced one of the highest rates of invasive *H influenza* type b disease. Hib was the most common cause of meningitis in children. Alaska Natives children <5 years of age experienced rates of invasive Hib disease ≥6 times higher than other similarly aged children in the United States (400-700 vs 60-100 per 100,000, respectively).[42]

After universal infant vaccination in 1991, *H influenza* type b disease among Alaska Native and non-Native children <5 years of age decreased by 94 percent and 96 percent respectively. During 2001-2004, the rate of *H influenza* type b disease in Alaska Native and non-Native children <5 years of age decreased to 5.4 and 0 per 100,000 per year, respectively (Figure 4). *H influenza* type b oropharyngeal carriage has decreased in Alaska Native children <5 years of age from 5.0 percent pre vaccine (before 1991) to 1.3 percent post vaccine. It is estimated that from 1992-2004, the Hib vaccine has prevented 479 Hib cases (95% CI 424-533) in Alaska Native children <5 years of age (average yearly population 12,975). In that same time period only 13 cases of non-b *H influenza* disease and 7 cases of nontypeable *H influenza* disease were reported in Alaska Native children <5 years of age.[41]

Introduction of PCV7 and Hib vaccines into the routine childhood vaccination schedule have both resulted in significant decreases in the rates of the respective disease in both Native and Non-Native children. Carriage of Hib and PCV7-serotype *S pneumoniae* has also decreased significantly after introduction of the vaccines. However, in Alaska Native children, the rates of replacement IPD by non-vaccine serotypes have increased significantly while the rates of non-vaccine serotype *H influenza* disease has remained very low.

There are no studies that examine the factors that contribute to the significantly higher rates of IPD in Alaska Native children verses non-Alaska Native children and children in the United States outside of Alaska. Environmental factors, such as household crowding, poorly ventilated homes, extremely cold weather, lack of breastfeeding, passive smoke exposure, low socioeconomic status, and limited indoor plumbing have been identified as possible causes.

Modern sanitation services (potable drinking water and safe wastewater disposal) are a cornerstone of public health progress and have contributed to decreased infectious disease morbidity and mortality. In 2000, 93.7 percent of Alaskan homes had complete sanitation, which ranked Alaska last among US states (US Census). The percentage of homes with in-home water service in many parts of rural Alaska is significantly lower. Many households in rural Alaska use outhouses or in-home waste containers commonly known as "honeybuckets" that require manual removal to a centralized waste disposal site or lagoon.

A study done by the Arctic Investigations Program, National Center for Infectious Diseases, CDC[43] investigated the relationship between the presence of in-home piped water and wastewater services, and hospitalization rates for respiratory tract, skin, and gastrointestinal tract infections in rural Alaska. Overall, 73 percent of homes in the study area (southwestern Alaska) had in-home water service (range by region: 57% to 100%). Over 95 percent of the residents of this study area are Alaska Native.

Higher respiratory and skin infection rates were associated with a lack of in-home water service. Regions with a lower proportion of home water services had significantly higher hospitalization rates for pneumonia and influenza (RR = 2.5), skin or soft tissue infection (RR = 1.9), and respiratory syncytial vires (RR = 3.4 among those younger than 5 years) than did higher-service regions. Within one region, infants from villages with less than 10 percent of homes with in-home water service had

higher hospitalization rates for pneumonia (RR = 1.3) and respiratory syncytial virus (RR = 1.2) than did infants from villages with more than 80 percent served. Outpatient *Staphylococcus aureus* infections (RR = 5.1, all ages) and skin infection hospitalizations (RR = 2.7, all ages) were higher in low-service than in high-service villages.

Another study conducted by the Arctic Investigations Program[44] on risk factors for severe respiratory syncytial virus (RSV) infection among Alaska Native children may be applicable to IPD. Similar to their rates of IPD infection, Alaska Natives in the Yukon-Kuskokwim Delta experience the highest annual RSV hospitalization rates in the world (156 per 1000 infants <1 year of age). This investigation was a case-control study of a remote region of southwestern Alaska with 204 Alaska Native hospitalized patients <3 years of age matched with 338 control patients. Control subject were children who had not been hospitalized for RSV infection matched to patients by age and village.

Breastfeeding was associated with a lower risk of RSV hospitalization (OR 0.34), whereas underlying medical conditions (primarily prematurity) were associated with increased risk (OR: 6.25). Environmental factors associated with a higher risk of hospitalization included household crowding (4 or more children in the household and crowding index [people per room] ≥2).

Conclusions from this study of a region with extremely high risk of RSV hospitalization are that several measures, such as encouraging breastfeeding and reducing household crowding, could reduce the risk of hospitalization attributable to RSV.

Under antibody selective pressure, pneumococci can be expected to quickly evolve to circumvent vaccines that contain a limited number of serotypes. The only long-term solution to the problem is the development of a vaccine containing one or several protective protein antigens from pneumococcus.[45]

Research is ongoing regarding development of alternative pneumococcal vaccines. Investigators are evaluating possible roles of conserved pneumococcal proteins (e.g. pneumolysin, surface protein A, or surface adhesion A) as antigens that have potential to provide broad protection against disease caused by pneumococcal serotypes.[46, 35] Use of other peptides or pneumococcal proteins as carriers in conjugate vaccines is also being studied. Additionally, alternative routes of delivery including intranasally and orally administered vaccines are under investigation.[47, 48]

Conclusion

The success of PCV7 in Alaska had lead to the near elimination of PCV7-serotype disease and elimination of a health disparity. However, for Alaska Native children there now exists a significantly elevated risk for IPD from serotypes not contained in PCV7. The demonstration of replacement IPD in Alaska Native children may signify a limit to the usefulness of PCV7 and emphasizes the importance of developing extended valency vaccines or vaccines not dependent on serotype-specific prevention. The increase in replacement IPD also highlights the need for continued surveillance and other epidemiological investigations to monitor the effects of pneumococcal vaccines.

In rural Alaska, basic improvements in housing, access to treated running water, instillation of sewage disposal and treatment facilities and improved economic opportunity would have far-reaching beneficial health effects. Although PCV7 has eliminated the disparity in vaccine-type IPD, we are likely to continue to see health disparities among Alaska Natives until those disparities in living conditions are also eliminated.

Table I. Rates of Invasive *Streptococcus Pneumoniae* by Time Period, Age Group, and Vaccine Serotype in Alaska Natives and non-Natives, 1995-2006*

	Rate per 100 000 (No.)					
	Native Alaskans			Non-Native Alaskans		
Age, y	1995-2000	2001-2003	2004-2006	1995-2000	2001-2003	2004-2006
Conjugate vaccine serotypes: 4, 6B, 9V, 14, 18C, 19F, and 23F						
<2	275.3 (84)	23.4 (4)	10.6 (2)	101.3 (86)	20.6 (9)	2.3 (1)
2-4	47.0 (21)	0	0	13.6 (17)	7.4 (5)	0
5-17	5.9 (12)	1.0 (1)	0	1.0 (6)	2.5 (8)	0.6 (2)
18-44	6.0 (16)	5.7 (8)	2.0 (3)	4.1 (50)	1.1 (7)	0.8 (5)
≥45	14.5 (22)	13.4 (11)	4.3 (4)	11.4 (102)	7.1 (35)	2.2 (12)
Total	22.3 (155)	6.5 (24)	2.3 (9)	8.9 (261)	4.1 (64)	1.3 (20)
Nonconjugate vaccine serotypes						
<2	95.1 (29)	99.3 (17)	228.6 (43)	23.6 (20)	29.7 (13)	39.0 (17)
2-4	13.4 (6)	8.7 (2)	39.6 (10)	4.0 (5)	7.4 (5)	13.9 (10)
5-17	8.3 (17)	5.7 (6)	7.6 (8)	2.5 (15)	1.6 (5)	2.2 (7)
18-44	16.2 (43)	17.9 (25)	23.1 (34)	3.6 (43)	2.9 (18)	4.2 (26)
≥45	32.3 (49)	53.5 (44)	71.2 (66)	10.5 (94)	6.7 (33)	14.6 (80)
Total	20.7 (144)	25.6 (94)	41.4 (161)	6.1 (177)	4.8 (74)	8.7 (140)
All cases						
<2	403.2 (123)	134.3 (23)	244.6 (46)	135.5 (115)	52.6 (23)	43.6 (19)
2-4	73.9 (33)	13.0 (3)	39.6 (10)	19.2 (24)	16.3 (11)	15.3 (11)
5-17	15.7 (32)	8.6 (9)	7.6 (8)	3.8 (23)	4.7 (15)	2.8 (9)
18-44	25.6 (68)	25.1 (35)	27.2 (40)	9.1 (110)	4.8 (30)	6.2 (38)
≥45	56.6 (86)	74.2 (61)	80.9 (75)	24.3 (217)	16.3 (80)	18.4 (101)
Total	49.1 (342)	35.7 (131)	46.0 (179)	16.7 (489)	10.2 (159)	11.1 (178)

*Disease caused by unknown serotypes accounted for 12.6% of invasive pneumococcal disease cases from 1995 through 2000, 9.9% of cases from 2001 through 2003, and 5.0% of cases from 2004 through 2006. Data for 1995 through 2003 were previously published10; however, some numbers and rates may be slightly different in this article because of updated information for this period.

Table II. Heptavalent protein-polysaccharide pneumococcal conjugate vaccine (PCV7)–type colonization among persons colonized with *Streptococcus pneumoniae,* by age class and year, Alaska, 1998–2004.

Age class,	Persons colonized with PCV7-type pneumococci, *n/N* (%)[a]					
Years	At baseline[b]	In 2001	In 2002	In 2003	In 2004	*P*[c]
<5	209/377 (55.4)	54/154 (35.1)	31/145 (21.4)	18/165 (10.9)	9/189 (4.8)	<.0001
18–24	30/80 (37.5)	17/64 (26.6)	11/63 (17.5)	7/102 (6.9)	5/106 (4.7)	<.0001
25–34	21/66 (31.8)	10/67 (14.9)	14/53 (26.4)	4/92 (4.4)	4/88 (4.6)	<.0001
35–44	14/69 (20.3)	12/64 (18.8)	8/69 (11.6)	8/99 (8.1)	4/86 (4.7)	.01
>45	13/60 (21.7)	8/71 (11.3)	3/81 (3.7)	5/120 (4.2)	4/97 (4.1)	.0001
All >18	78/275 (28.4)	47/266 (17.7)	36/266 (13.5)	24/413 (5.8)	17/377 (4.5)	<.0001

[a] No. of persons colonized with PCV7-type *S. pneumoniae*/no. of persons colonized with *S. pneumoniae* (% of persons colonized with PCV7-type *S. pneumoniae*).
[b] 1998–2000.
[c] By 2 test of trend.

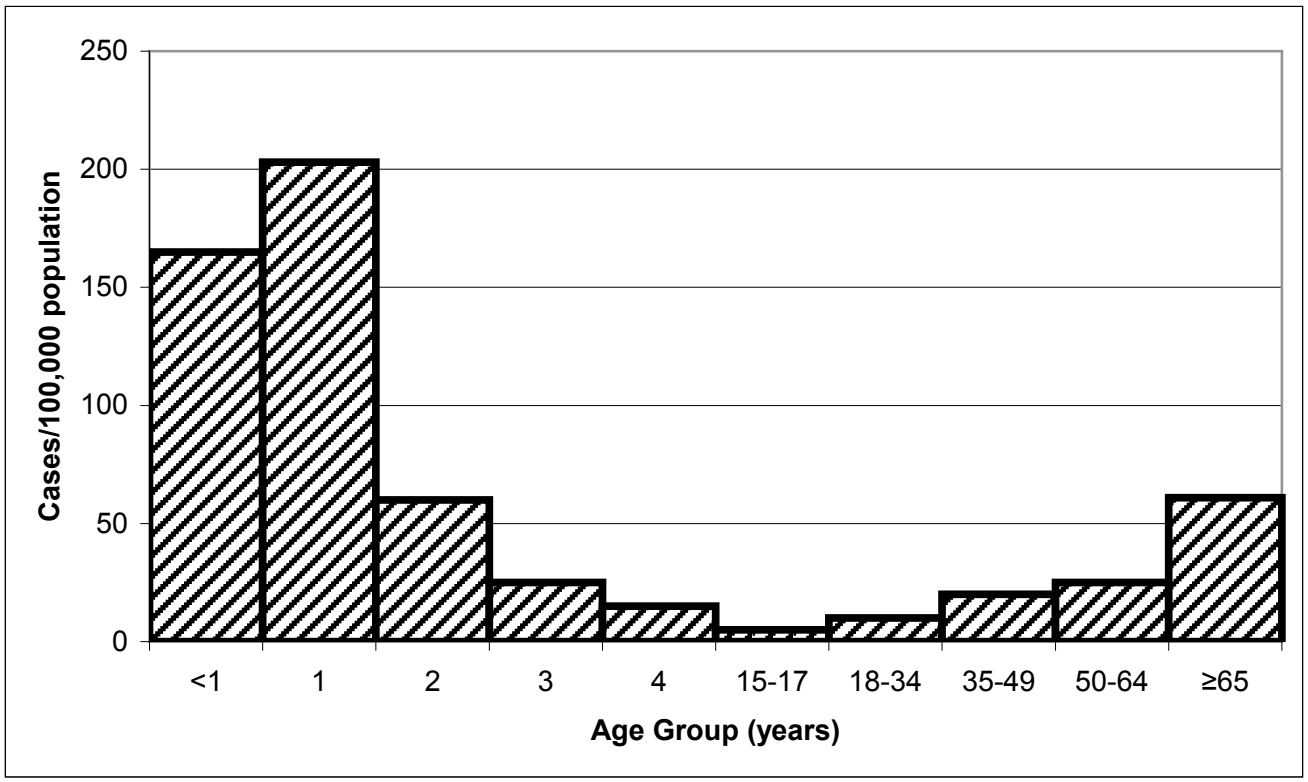


Figure I. Rates of invasive pneumococcal disease by age group - United States, 1998.

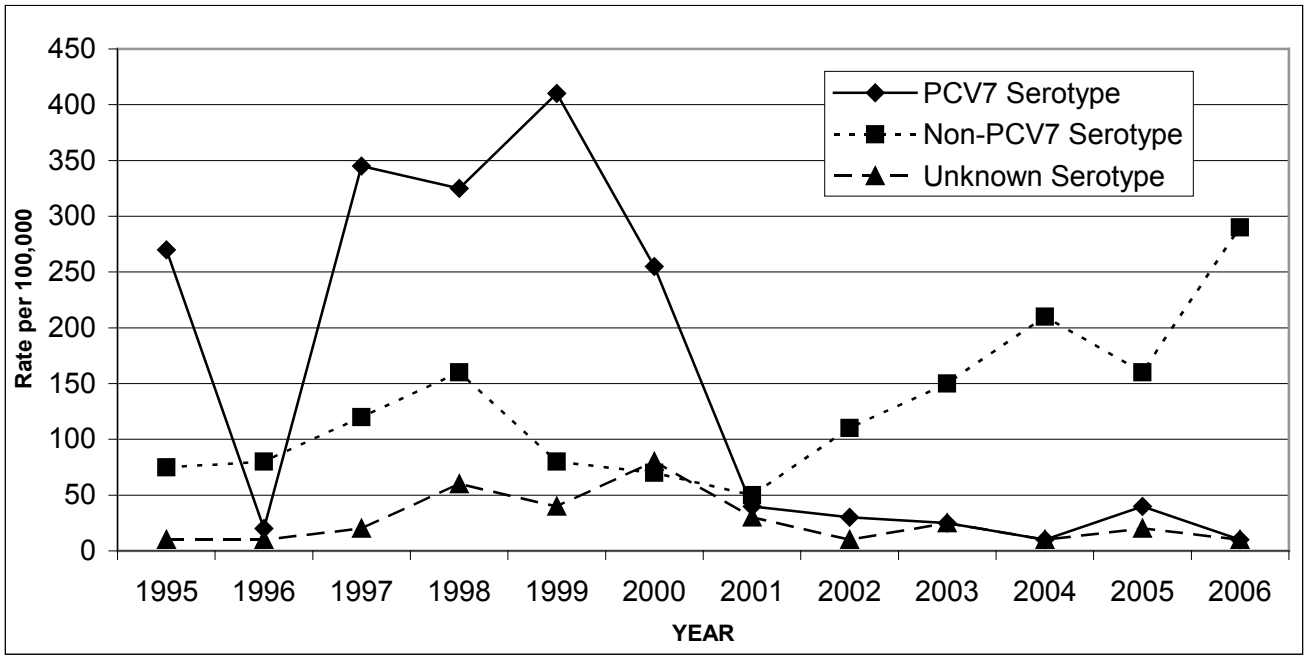
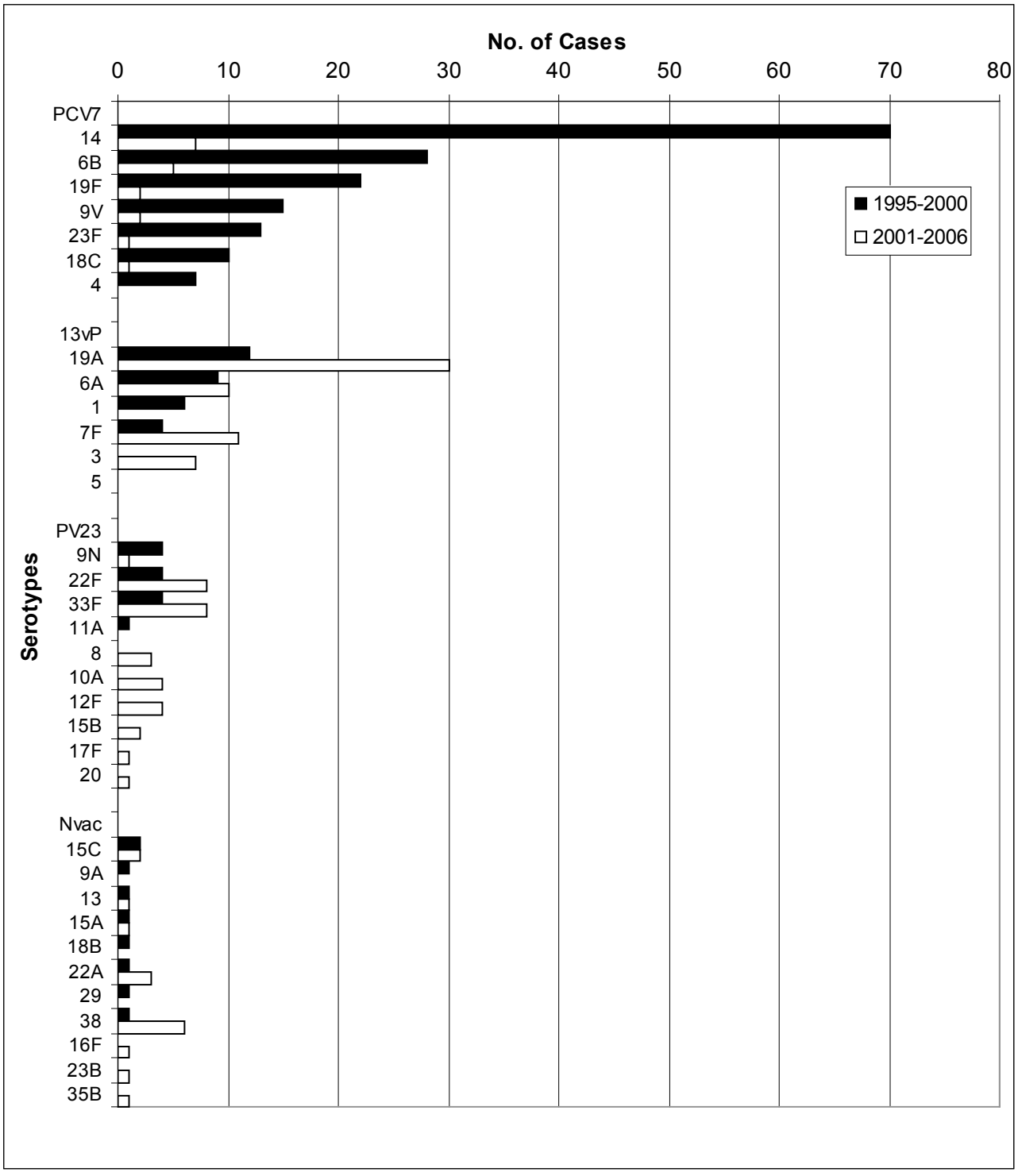


Figure II. Rates of Invasive Pneumococcal Disease in Alaskan Native Children Younger Than 2 years and Serotype, 1995-2006.



PCV7 - 7-valent pneumococcal conjugate vaccine
13vP – 13-valent pneumococcal conjugate vaccine under development
PV23 – 23-valent polysaccharide vaccine
Nvac – Non vaccine serotypes

Figure III. Cases of Invasive Pneumococcal Disease by Serotype Among Alaska Children Younger Than 2 years, 1995-2000 and 2001-2006.

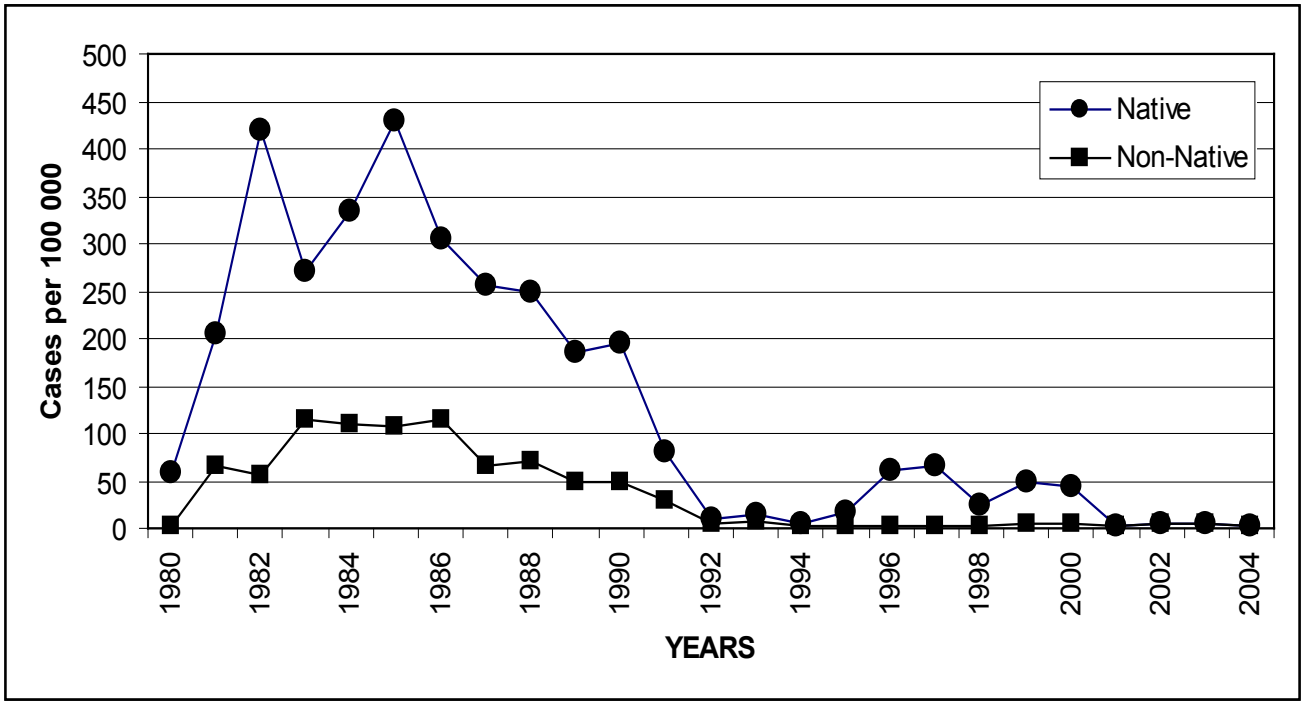


Figure IV. Invasive Hib disease rates per 100,000 in Alaska Native and non-Native children aged <5 years, 1980-2004.

References

1. Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C. Estimates of world-wide distribution of child deaths from acute respiratory infections. *Lancet.* 2002; 2: 25–32.

2. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCs) Report, Emerging Infections Program Network (EIP), *Streptococcus pneumoniae*, 1998. Atlanta, GA: US Department of Health and Human Services, CDC 1999. Available at <http://www.cdc.gov/ncidod/dbmb/abcs/spneu98.pdf>.

3. Davidson M., et al. The epidemiology of invasive pneumococcal disease in Alaska, 1986-90: ethnic differences and opportunities for prevention. *J Infect Dis.* 1994;170:368.376.

4. Rudolph KM, Parkinson AJ, Reasonover Al, Bulkow LR, Parks DJ, Butler JC. Serotype distribution and antimicrobial resistance patterns of invasive isolates of Streptococcus pneumoniae: Alaska, 1991–1998. *J Infect Dis*. 2000;182:490–6.

5. Poehling KA, et al. Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. *JAMA*. 2006;295:1668-1674.

6. Hennessy TW, Singleton RJ, et al. Impact of heptavalent pneumococcal conjugate vaccine on invasive disease, antimicrobial resistance and colonization of Alaska Natives: progress towards elimination of a health disparity. *Vaccine.* 2005;23:5464-5473.

7. Moore MR et al. Impact of conjugate vaccine on community-wide carriage of nonsusceptible *Streptococcus pneumoniae* in Alaska. *J Infect Dis*. 2004; 190:2031–2038.

8. Centers for Disease Control and Prevention. Preventing pneumococcal disease among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2000;49(RR-9):1-35.

9. Brueggeman AB, Peto TE, Crook DW, Butler JC, Kristinsson KG, Spratt BG. Temporal and geographic stability of the serogroup-specific invasive disease potential of *Streptococcus pneumoniae* in children. *J Infect Dis.* 2004;190:1203-1211.

10. Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 1997;46(No. RR-8):1-24.

11. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr Infect Dis. J.* 2000; 19: 187–95.

12. Miernyk KM, Parkinson AJ, Rudolph KM, et al. Immunogenicity of a heptavalent pneumococcal conjugate vaccine in Apache and Navaho Indian, Alaska Native, and non-native American infants aged ≥2 years. *Clin Infect Dis.* 2000;31:34-41.

13. Centers for Disease Control and Prevention. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease-United States, 1998-2003. *MMWR Morb Mortal Wkly Rep.* 2005;54:893-897

References (continued)

14. Singleton RJ, et al. Invasive pneumococcal disease caused by nonvaccine serotypes among Alaska Native children with high levels of 7-valent pneumococcal conjugate vaccine coverage. *JAMA*. 2007;297:1784-1792.

15. Centers for Disease Control and Prevention. National, state, and urban area vaccination coverage among children aged 19-35 months-United States, 2004. *MMWR Morb Mortal Wkly Rep.* 2005;54:717-21.

16. O'Brien KL, Moulton LH, Reid R, et al. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomized trial. *Lancet*. 2003;362:355-361.

17. Singleton RJ, Butler JC, et al. Invasive pneumococcal disease epidemiology and effectiveness of 23-valent pneumococcal polysaccharide vaccine in Alaska Native adults. *Vaccine.* 2007;25:2288–2295.

18. Butler JC, Bulkow LR, Parks DJ, Parkinson AJ. Epidemiology of pneumococcal bacteremia and meningitis during the first five years of life in Alaska: implications for conjugate pneumococcal vaccine use. In: Proceedings of the Second Annual International Symposium on Pneumococcus and Pneumococcal Disease. 2000.

19. Bogaert D, De Groot R, Hermans PW. Streptococcus pneumoniae colonization: the key to pneumococcal disease. Lancet Infect Dis 2004; 4:144–54.

20. Huang SS, Platt R, Rifas-Shiman SL, et al. Post-PCV7 changes in colonizing pneumococcal serotypes in 16 Massachusetts communities, 2001 and 2004. *Pediatrics.* 2005;116:e408.

21. Millar EV, O'Brein KL, Watt JP, et al. Effect of community-wide conjugate pneumococcal vaccine use in infancy on nasopharyngealo carriage through 3 years of age: a cross-sectional study in a high-risk population. *Clin Infect Dis.* 2006;43:8.

22. Crook DW, Brueggeman AB, Sleeman KL, Peto TEA. Pneumococcal carriage. In: Tuomanen EI, Mitchell TJ, Morrison DA, Spratt BG, eds. *The pneumococcus*. Washington, DC: American Society for Microbiology Press, 2004:136–47.

23. Hendley JO, Sande MA, Stewart PM, Gwaltney JM Jr. Spread of Streptococcus pneumoniae in families. I. Carriage rates and distribution of types. *J Infect Dis* 1975; 132:55–61.

24. Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. *N Engl J Med* 2000; 342:681–9.

25. Hammitt LL, et al. Indirect effect of conjugate vaccine on adult carriage of *Streptococcus pneumoniae:* An explanation of trends in invasive pneumococcal disease. *J Infect Dis*. 2006; 193:1487–1494.

References (continued)

26. Dagan R, Givon-Lavi N, Zamir O, Fraser D. Effect of a nonavalent conjugate vaccine on carriage of antibiotic resistant Streptococcus pneumoniae in day-care centers. *Pediatr Infect Dis J.* 2003;22:532- 540.

27. Obaro SK, Adegbola RA, Banya WA, Greenwood BM. Carriage of pneumococci after pneumococcal vaccination. *Lancet*. 1996;348:271-272.

28. McEllistrem MC, Adams JM, Patel K, et al. Acute otitis media due to penicillin non-susceptible *Streptococcus pneumoniae* before and after the introduction of the pneumococcal conjugate vaccine. *Clin Infect Dis*. 2005;40:1738-1744.

29. Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman KP. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. *J Infect Dis*. 1999;180:1171- 1176

30. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med*. 2001;344:403-409.

31. Ghaffar F, Barton T, Lozano J, et al. Effect of the 7-valent pneumococcal conjugate vaccine on nasopharyngeal colonization by *Streptococcus pneumoniae* in the first 2 years of life. *Clin Infect Dis*. 2004;39:930-938.

32. O'Brien KL, Weatherholtz R, Millar EV, et al. Replacement invasive pneumococcal disease 9 years after introduction of PCV among a population at high risk for IPD: the Navajo Experience. In: *Program and abstracts of the 5th Annual International Symposium on Pneumococcus and Pneumococcal Disease*; April 2-6, 2006; Alice Springs, Australia. Abstract P04.17: 189.

33. Krause VL, Cook H, Selvey CE. Impact of 7vPCV and 23vPPV booster in eligible children in the Northern Territory of Australia: impressive, but not the total answer. In: Program and abstracts of the 5th International Symposium on Pneumococci and Pneumococcal Disease; April 2-6, 2006; Alice Springs, Australia. Abstract SY1.032006:55.

34. Regev-Yochay G, Dagan R, Raz M, et al. Association between carriage of *Streptococcal pneumoniae* and *Staphylococcus aureus* in children. *JAMA*. 2004;292:716.

35. Schrang SJ, Beall B, Dowell SF. Limiting the spread of resistant pneumococci: biological and epidemiologic evidence for the effectiveness of alternative interventions. *Clin. Microbiol Rev.* 2000;13:588-601.

36. Whitney CG, Farley MM, Hadler J, et al. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. *N Engl J Med*. 2000;343:1917-24.

37. Centers for Disease Control and Prevention. Emergence of antimicrobial-resistant serotype 19A *Streptococcus pneumoniae*--Massachusetts, 2001-2006. *MMWR Morb Mortal Wkly Rep.* 2007;56:1077.

References (continued)

38. O'Brien KL and R. Dagan. The potential indirect effects of conjugate pneumococcal vaccines. *Vaccine.* 2003;21:1815-1825.

39. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med.* 2003;348:1737–46.

40. Klugman KP. Vaccination: a novel approach to reduce antibiotic resistance. *Clin Infect Dis.* 2004;39:649.

41. Singleton RJ, Hammit L, et al. The Alaska Haemophilus influenza Type b Experience: Lessons in Controlling a Vaccine-Preventable Disease. *Pediatrics.* 2006;118:421-429.

42. Ward JI, Lum MK, Hall DB, Silimperi DR, Bender TR. Invasive *Haemophilus influenzae* type b disease in Alaska: background epidemiology for a vaccine efficacy trial. *J Infect Dis.* 1986;153:17-26.

43. Hennessy TW, Ritter, T, et al. The Relationship Between In-Home Water Service and the Risk of Respiratory Tract, Skin, and Gastrointestinal Track Infections Among Rural Alaska Natives. *Am J Public Health.* 2008;98:XXX-XXX.

44. Bulkow LR, Singleton RJ, et al. Risk Factors for Severe Respiratory Syncytial Virus Infection Among Alaska Native Children. *Pediatrics.* 2002;109:210-216.

45. Lee CJ, Banks SD, Li Jp. Virulence, immunity and vaccine related to *Streptococcus pneumoniae*. *Crit Rev Microbiol.* 1991;18:89.

46. Patton JC. Novel pneumococcal surface proteins: role in virulence and vaccine potential. *Trends Microbiol*. 1988;6:85-7.

47. Flanagan MP, Michael JG. Oral immunization with a *Streptococcal pneumoniae* polysaccharide conjugate vaccine in enterocoated microparticles induces serum antibodies against type specific polysaccharides. *Vaccine.* 1999;17:72-81.

48. Könen-Waisman S, Cohen A, Fridkin M, Cohen IR. Self-shock protein (hsp60) peptide serves in a conjugate vaccine against a lethal pneumococcal infection. *J Infect Dis.* 1999;179:403-13.

49. Tuomanen EI. Impact of universal infant immunization with pneumococcal (Streptococcus pneumoniae) conjugate vaccines in the United States. *UpToDate*. Ver 16.1. 2007.

Appendix A: Preventing Pneumococcal Disease Among Infants and Young Children.

Recommendations of the Advisory Committee on Immunization Practices (ACIP) – United States Centers for Disease Control and Prevention (CDC)

Summary

In February 2000, a 7-valent pneumococcal polysaccharide-protein conjugate vaccine (Prevnar,™ marketed by Wyeth Lederle Vaccines) was licensed for use among infants and young children. CDC's Advisory Committee on Immunization Practices (ACIP) recommends that the vaccine be used for all children aged 2-23 months and for children aged 24-59 months who are at increased risk for pneumococcal disease (e.g. children with sickle cell disease, human immunodeficiency virus infection, and other immunocompromising or chronic medical conditions). ACIP also recommends that the vaccine be considered for all other children aged 24-59 months, with priority given to a) children aged 24-35 months, b) children who are Alaska Native, American Indian, and African-American descent, and c) children who attend group day care centers. This report includes ACIP's recommended vaccination schedule for infants at ages 2, 4, 6 and 12-15 months. This report also includes a pneumococcal vaccination schedule for infants and young children who are beginning their vaccination series at an older age and for those who missed doses. In addition, this report updates earlier recommendations for use on 23-valent pneumococcal polysaccharide vaccine among children aged ≥2 years. Among children aged 24-59 months for whom polysaccharide vaccine is already recommended, ACIP recommends vaccination with the new conjugate vaccine followed, ≥2 months later, by 23-valent polysaccharide vaccine. Conjugate vaccine had not been studied for its use among persons aged ≥5 years. Persons aged ≥5 years who are at increased risk for serious pneumococcal disease should continue to receive 23-valent polysaccharide vaccine in accordance with previous ACIP recommendations.

Source: Centers for Disease Control and Prevention. Preventing pneumococcal disease among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2000;49(RR-9):1-35.